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Central Neurotransmitter Function and Its Behavioral Correlates in Man

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The past decade has witnessed a tremendous increase in knowledge towards understanding the function of various brain neurotransmitter substances in behavior. Experimental observations in animals, utilizing specific pharmacological agents, have enabled the development of certain hypotheses regarding neurochemical substrates of behavior. These have led to cautious applications of complementary studies in humans. As a result, several neurotransmitter-related hypotheses have been developed for the explanation of normal behavior, as well as of various abnormal behavior states in psychiatry and neurology. These hypotheses are currently undergoing extensive investigation.

Highlights of the above sequence of events are presented, in order to provide as general, yet extensive, an overview of the subject as possible. Examples are provided from both basic laboratory investigations and from clinical findings. Principles of brain neurotransmitter function and interactions are reviewed. Various neurotransmitter-related hypotheses of psychiatric and neurologic interest are introduced. Finally, the role that toxicants may have on behavior via alteration of brain neurotransmitter function is discussed, using the lead intoxicated animal as an illustrative example.

Introduction

An assessment of behavior, particularly that which is associated with changes in mood states, is, in itself, a difficult task. The problem becomes infinitely more complex when one couples that with attempts to understand and explain behavioral phenomena in humans by extrapolation from observations in animals. Any analysis of neurochemical phenomena and their correlation with behavioral function in humans, on the other hand, could be conducted more readily in human subjects, using available information obtained from experimental animals. Whereas animal behavior could be radically different from one species to another, neurochemical phenomena are generally reproducible across species in the mammalian system. Moreover, there exists a wide reservoir of neurochemical observations, obtained across a variety of mammalian species, which could serve as an important resource for extrapolation to man. For this reason, scientists have been encouraged during the past decade in their attempts to explain clinical observations on the basis of known neurotransmitter-related studies conducted on experimental animals. In fact, such correlations have been extended even further to include neurotransmitter-related hypotheses for the etiology of a variety of psychiatric states, including depression, mania and schizophrenia. Ingenious biochemical approaches have even been devised to study the validity of these hypotheses directly in man.

The goal of this paper is to review, in general terms, the neurotransmitter mechanisms operating in brain and to illustrate how central neurotransmitter function may be critical to the control and determination of behavior. The role of environmental toxicants in affecting behavior will also be analyzed in the context of this information. Because of the general nature of this article, references provided will be primarily review articles, in order to equip the reader with a broader literature base from which to obtain a more comprehensive coverage of the information at hand.

Neurotransmitters: An Overview

It is now generally believed that a number of endogenous compounds function as neurotransmitters in the central nervous system. These include the

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substances, norepinephrine (NE), dopamine (DA), 5-hydroxytryptamine (serotonin, 5HT), acetylcholine (ACh), γ-aminobutyric acid (GABA), phenylethylamine, histamine, glycine, glutamic acid, aspartic acid, taurine, and a number of peptides such as substance P, and the enkephalins (*1*).

Neurotransmitters are stored in nerve terminals and are believed to be released from these terminals following stimulation of the nerve. A very complex machinery is known to exist which is responsible for the synthesis of these transmitter agents, their storage within the nerve terminals, and their release upon demand of the organism. This machinery involves a variety of steps, including energy-dependent transport mechanisms and sophisticated enzyme reactions (*2, 3*). These steps have been extensively investigated, and are now well understood in reference to the neurotransmitter substances, ACh, NE, DA, and 5HT. Active research is presently underway toward establishing factors involved in the synthesis, storage, degradation and release of the other neurotransmitter candidates as well.

Certain criteria have been established which, when fulfilled, would qualify a compound for consideration as a bona fide central neurotransmitter agent. Specifically, the substance should be shown to exist as an endogenous compound. Enzymes for its synthesis and degradation and mechanisms for its inactivation should be demonstrated within the organism. Last, but not least, pharmacologic agents known to alter the activity resulting from stimulation of nerve terminals containing the suspected neurotransmitter substance should induce the same effect in response to administration of the suspected compound from an external source. It is interesting to note that, to date, only ACh has fulfilled all the established criteria for a central neurotransmitter agent. The weight of evidence favoring a central neurotransmitter role for NE, DA, and 5HT is, however, also considerable. Some of the other mentioned compounds are known as "putative" neurotransmitters, since available data provide for these agents evidence of only a partial fulfillment of the named criteria. Further supportive data favoring the role of these compounds as central neurotransmitter agents are forthcoming. Investigative efforts in this area of research are presently progressing with vigor (*1*).

The distribution in brain of the various neurotransmitter agents is predicated by the neuronal networks existing in the brain. Different nerve tracts connect various anatomical locations in the brain. Many are known; some have yet to be discovered. In general, nerves containing a specific neurotransmitter substance will cluster in tracts. The area in which the tract terminates would be rich in nerve terminals containing the specific neurotransmitter substance, and consequently the measured concentration of the neurotransmitter would be high. More than one nerve tract will innervate a particular brain area. Consequently, more than one neurotransmitter substance could be identified and measured in this area. For example, DA containing neurons have been shown to project from the substantia nigra to the caudate nucleus in brain (*4–6*). As would be predicted from this observation, the caudate nucleus contains high concentrations of the neurotransmitter, DA. The caudate nucleus, however, is also rich in ACh (*7*). It is, therefore, evident that cholinergic (i.e., containing ACh) nerve endings are concentrated in the caudate nucleus, as well as DA-ergic nerve endings. In fact, it has been demonstrated that a major portion (although not all) of cholinergic neurons both originate and terminate in the caudate nucleus; i.e., they exist primarily as interneurons (*8*). The task of identification, anatomic localization and quantitation of the various neurotransmitter substances has been the subject of extensive investigation over the past two decades and has resulted in a number of excellent reference sources of information (*4, 5, 8–13*).

The very fact that more than one category of neurons does terminate in a specific brain area has an important telic reason. Intricate interactions exist between the various neuronal terminals to be found in brain areas. Nerve terminals originating from one projection or tract are postulated to impinge on nerve terminals and/or on dendrites from cell bodies of nerves from one or several other projections or tracts. This results in an interaction between the neurons involved. Consider the following simple hypothetical example of one neuronal tract impinging on another tract. Electrical stimulation of the first nerve tract would result in mobilization and release of the neurotransmitter from the nerve terminals of that tract. The released transmitter substance would then diffuse across the synaptic clefts existing between the originating nerve terminals and the so-called "effector" nerve terminals and/or dendrites of the second tract which is to be influenced by the released transmitter. The sum total of this sequence would be the transmission of information from one nerve tract to another as a combined result of electrical and neurochemical phenomena. The neurotransmitter would then interact with receptors on the postsynaptic site and trigger a response which would result either in the activation or inhibition of transmission of an impulse on the effector side. Whether activation or inhibition occurs would depend upon a complex sequence of events related to the chemical nature of the neurotransmitter substance, and the physiological properties of the effector neuron.

A similar interaction actually occurs between DA-containing nerve terminals within the caudate nucleus, and the cholinergic interneurons within the same brain area. The DA-containing nerve terminals appear to impinge on dendrites of the cell bodies of the cholinergic interneurons (*14*). Moreover, DA appears to exert a tonic inhibitory effect on the postsynaptic receptor site (*15–18*). Consequently, stimulation of the release of DA from these nerve terminals would result in the reduction of activity of the ACh-containing neurons in the caudate nucleus. Alternatively, if one diminishes the afferent influence of the DA-containing neurons in the caudate nucleus (e.g., by blocking the postsynaptic DA-specific receptors with a pharmacologic "neuroleptic" agent), one would release the tonic inhibitory influence of these neurons on the cholinergic interneurons. The end result of this action would be a reduction in DA activity and a concomitant increase in ACh activity within the caudate nucleus. The cholinergic interneurons, in turn, are known to impinge on other neurotransmitter systems which extend out of the caudate nucleus to other brain areas (*19, 20*).

Thus, there exists a sequence of interacting mechanisms in the brain, each subject to the specific characteristics of the neurotransmitter mechanism involved. Moreover, a disturbance of this sequence of systems would trigger a chain reaction and attempts by the brain to restore matters back to normal. The complexity of this picture is compounded when one considers the number of intertransmitter interactions which could and do exist *in vivo;* also, the number of brain areas which are involved in these interactions. Different brain areas control different functions in our bodies. Consequently, an imbalance, whether endogenously or drug-induced, even in a very specific brain area, may result in a series of physiological as well as neurological and/or mental aberrations. The nature and extent of such aberrations would depend upon the neuronal circuitry which hooks up the particular affected brain area with other parts of the brain.

Neurotransmitter Interactions and Their Clinical Correlates

In spite of this existing complexity, in most situations a deviation from normal physiologic function has been attributed primarily (if not entirely) to an imbalance in one particular neurochemical system, or sometimes between two neuronal networks in the brain. For example, the caudate nucleus is very important *in vivo* for the control of movement. As has already been pointed out earlier, a seesaw-type interaction exists under natural conditions between DA and ACh in the caudate nucleus. An imbalance in this interaction appears to be the cause of a number of neurologic disorders. Specifically, Parkinson's disease results from a deficiency of the DA-containing neurons, and a consequent hyperactivity of the cholinergic interneurons. On the other hand, Huntington's chorea and tardive dyskinesias appear to result from an exacerbation of DA influence, and a parallel reduction in cholinergic activity in the caudate nucleus. This is evident from indirect studies demonstrating that pharmacologic manipulations through selective blockade and/or activation of the appropriate neuronal activity result in an alleviation of the clinical syndrome (*20*).

One must, of course, always keep in mind that other neurotransmitter systems will also be involved in the etiology of the above syndromes, for the reasons already elaborated earlier on. Current neurotransmitter hypotheses such as those described in the clinical situations mentioned above are gross simplifications. They are, nevertheless, necessary for the purpose of initiating some type of systematic approach to the treatment of these clinical syndromes.

Similar logic and reasoning as that applied earlier to the analysis of neurochemical correlates of neurologic disorders is also applicable in the evaluation of hypotheses of neurotransmitter-related correlates of mood and behavior in humans. By extrapolation from animal research, various investigators have attempted to understand human behavior in terms of neurotransmitter function, or often, dysfunction. An understanding of the mode of action of specific, effective psychotropic agents at the level of the nerve terminal has been instrumental in interpreting the mode of action of the same drugs in human brain. Thus, for example, amphetamine, at early stages of ingestion, has been shown, at the neuronal level, to stimulate the release of catecholamines (i.e., NE and DA) from their nerve terminals (*21, 22*) and to increase availability of DA and NE, as well as 5HT, at their corresponding postsynaptic receptor sites (*21, 23–26*). Reserpine, on the other hand, results in depletion of NE, DA and 5HT stores from their corresponding nerve terminals (*27*). In humans and experimental animals, amphetamine causes euphoria, excitation, and hyperactivity, while reserpine generally induces a state of depression and lethargy.

These findings, in combination with observations indicating that other pharmacological agents known to increase NE and/or 5HT activity at the postsynaptic receptor site [e.g., the tricyclic antidepressants (*23, 26, 28–31*) and the monoamine oxidase inhibitors (*32*)] are antidepressant agents which will also induce behavioral excitation in experimental animals, have led to the development of the so-called "catecholamine hypothesis of affective disorders." Expressed in simple terms, this hypothesis states that improvement in mood is related to increased stimulation of NE receptors in areas in brain which control mood and emotion; alternatively, a reduction in stimulation of the same NE receptors would result in dysphoria (*33–35*).

This hypothesis, originally expressed in 1965, has had its share of detractors as well as supporters. Its major contribution, nevertheless, is in the fact that it has opened up a new dialogue. This hypothesis has served to encourage other investigators to explain other clinical observations on the basis of known neurotransmitter-related studies conducted on experimental animals, following administration of pharmacological agents with known effect on the activity of the various endogenous neurotransmitters. No matter how simplistic these hypotheses might turn out to be, and whether or not they are eventually borne out to be true, such hypotheses invariably will stimulate more research in the area. The outcome of such research could only lead to a better understanding of the various clinical entities involved, and to the development of improved drugs and/or methods of treatment of these syndromes.

At the present time, a number of neurotransmitter-related hypotheses of human psychiatric syndromes have been proposed, each involving one or more specific neurotransmitter substance. These are summarized in Table 1. Note that all these hypotheses are fairly recent. The pros and cons of these various hypotheses are discussed in greater detail in the corresponding references as well as in the excellent book by Barchas et al. (*46*).

Table 1. Current list of proposed neurotransmitter-related hypotheses in psychiatry.

Primary transmitter(s) involved	Psychiatric syndrome(s) implicated	References
DA	Schizophrenia	(*36, 37*)
Methylated derivatives of tryptamine, 5HT (transmethylation H_o)	Schizophrenia	(*38*)
GABA	Schizophrenia	(*39*)
Phenylethylamine	Schizophrenia	(*40, 41*)
ACh / DA (balance H_o)	Schizophrenia/ depression	(*42, 43*)
NE (catecholamine H_o)	Depression	(*33–35, 44*)
5HT (indoleamine H_o)	Depression	(*45*)

Approaches Used in Assessing Central Neurotransmitter Function in Man *in vivo*

One of the major difficulties in testing these various hypotheses is inherent in the limitations imposed on any type of research which can ethically be conducted in humans. Nevertheless, several approaches have been utilized successfully while monitoring readily accessible tissues from living human subjects, namely urine, blood and cerebrospinal fluid (CSF). Since it is impossible to sample brain tissue in living humans, the next alternative is to monitor precursors, metabolites, and enzymes responsible for synthesis and degradation of the various neurotransmitter substances, in any or all of the above mentioned available fluids. Information obtained from such analyses, albeit deductive, may nevertheless provide an index of concomitant neurotransmitter function in brain. This type of logic has been applied to the investigation of a number of the neurotransmitter-related hypotheses listed in Table 1.

A representative list, which is by no means comprehensive, includes analyses in human subjects of the endogenous metabolite of NE, 3-methoxy-4-hydroxyphenylglycol (MHPG) in CSF, urine, and plasma (*44, 47*); of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5HIAA), the metabolites of DA and of 5HT, respectively, in CSF (*44, 45*); of ACh and of choline, the endogenous precursor of ACh, in blood, plasma, and RBC (*48–50*); of the NE and DA-related enzymes, dopamine-β-hydroxylase, catechol-*O*-methyltransferase, and monoamine oxidase in serum, RBC, and platelets, respectively (*44*), and others. Attempts have been conducted to determine whether a specific variety of mental illness may be indicated by a deviation from normal values in one or more of the parameters tested. These findings are then interpreted as being either supportive or contradictory to the tested neurotransmitter-related hypothesis.

Understandably, all the existing hypotheses to date are still undergoing the growing pangs of criticism and skepticism; consequently they are resulting in more efforts at documentation and consolidation of data. Nevertheless, these various hypotheses have served a heuristic value in stimulating a tremendous wave of both preclinical, as well as clinical research within the past decade. The products of this labor are yet forthcoming.

Do Environmental Toxicants Influence Central Neurotransmitter Function?

The subject matter of this paper is of major importance to investigators interested in behavioral consequences of neurotoxicity. Consider, for example the neurochemical effects of lead toxicity in rodents. Chronic lead exposure has generally been shown to increase central nervous system metabolism of the neurotransmitters DA and NE; on the other hand, central activity and metabolism of ACh appear to be diminished following chronic lead exposure (*51*). Thus, more than one neurotransmitter is affected in parallel as a result of exposure of the individual to the toxicant. Moreover, the effect is not necessarily similar in the case of each neurotransmitter substance. It has furthermore been suggested by several investigators that the lead intoxicated rodent may be used as a reliable animal model for minimal brain dysfunction (MBD), a syndrome also commonly known as hyperactivity in humans. This suggestion is based primarily on existing information regarding a variety of factors. Specifically, these include the measured neurological sequelae of lead toxicity in mice and rats; the similarity in a paradoxical response of both MBD patients and lead-treated animals to the pharmacological agents amphetamine and phenobarbital; and the clinical observation of a possible correlation in young children between the incidence of MBD, and of subclinical toxicity in these same children as a result of exposure to high concentrations of lead (*51, 52*).

Other environmental toxicants have also been shown to induce neurologic symptoms similar to those seen during neurotransmitter imbalances in humans. For example, chronic manganese poisoning has been implicated on the development of a Parkinsonian syndrome in humans and monkeys (*53*). Moreover, cobalt has been shown to induce epilepsy following its cortical implantation in experimental animals (*54*). Both toxicants have been shown to alter neurotransmitter mechanisms in brain while inducing their degenerative effects (*53, 54*). Excellent reviews on the neurologic effect of mercury (*55*) and of a variety of other metals (*56*) have also been published recently.

Based on this information, it is plausible that the effects of other environmental toxicants may also be significantly tied in with alterations in central neurotransmitter function. It therefore may not be too speculative to propose, on the basis of the concepts discussed in this paper, that certain clinically observed conditions of mood alteration, and even certain degenerative organic syndromes, may be the result of insidious, but definite effects of environmental toxicants on humans.

Summary

By design, the information in this article has been presented as a very general overview. Each new aspect, discussed here in such simple terms, has been the result of complex and lengthy investigations. Some of the points reported here are still a subject of controversy and intensive research. Thus, it is hoped that by no means will the reader of this article develop the impression that the question of central neurotransmitter function and its behavioral correlates in mammals, and particularly in man, is a straightforward and clearcut issue.

On the other hand, it is just as important to emphasize that this area of investigation has witnessed tremendous strides within the past decade, in terms of elucidating some of the issues described in this paper. This is attributable primarily to two key factors. With the recent development of sophisticated methodological approaches one can now conveniently measure quantitatively, and with high specificity, very low concentrations of neurotransmitters, their metabolites, and their related enzymes. This feature, plus an ever-growing dialogue between basic and clinical researcher, are paving the way for the development of an increasing number of clinically oriented research projects, with the eventual goal of understanding more about endogenous factors contributing to behavioral aberrations, and consequently, to their successful treatment in humans.

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